RNA metabolism

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First demonstration of miRNA-dependent mRNA decay

MicroRNAs (miRNAs) are important regulators of gene expression. Their function and roles were first discovered in the development of the worm *Caenorhabditis elegans*, and later shown to occur in all multicellular organisms. miRNAs function by guiding effector proteins through the recognition of complementary miRNA sequences in target mRNAs. In most animals, miRNAs form imperfect hybrids with sequences in the 3′ untranslated regions (3′UTRs) of mRNAs; the 'seed' region of the miRNA ensures targeting specificity. Nowadays, we know that this interaction leads to the recruitment of a protein complex that represses translation and causes deadenylation and degradation of target mRNAs.

By contrast, the original model that was proposed to explain the mechanisms underlying miRNA functions postulated that the mRNA remains stable after miRNA binding, and that gene repression occurs only at the level of translation. This conclusion was based on initial findings that miRNAs regulated the levels of target proteins, but not of target mRNAs. This model dominated the field until the publication of a key study by Amy Pasquinelli's lab in 2005.

Pasquinelli and her team showed that two miRNAs in *C. elegans* — let-7 and lin-4 — trigger degradation of their imperfectly complementary mRNA targets (*lin-41*, *lin-14* and *lin-28*). This conclusion was widely accepted thanks to the use of the same experimental system as the one used to establish the initial model and owing to the technical rigour of the work. The authors used northern blotting and reverse transcriptase quantitative PCR (RT–qPCR) to compare levels of miRNA targets across developmental stages, during which miRNA expression changes, and also between miRNA-mutant and wild-type worms. They ruled out transcriptional gene regulation as a mechanism of miRNA function using chromatin immunoprecipitation experiments. Finally, the authors confirmed mRNA degradation by carrying out *lacZ* reporter experiments with the wild-type 3′UTR of *lin-41* or with a mutant 3′UTR, in which the let-7-binding sites were deleted.

> **"This work... triggered further mechanistic studies of miRNAs"**

This work was followed up by numerous studies showing the degradation of miRNA targets in other organisms and triggered further mechanistic studies of miRNAs. Research in subsequent years provided an understanding of how miRNAs cause mRNA degradation and translation repression and how these two mechanisms contribute to overall miRNA-mediated gene repression.

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